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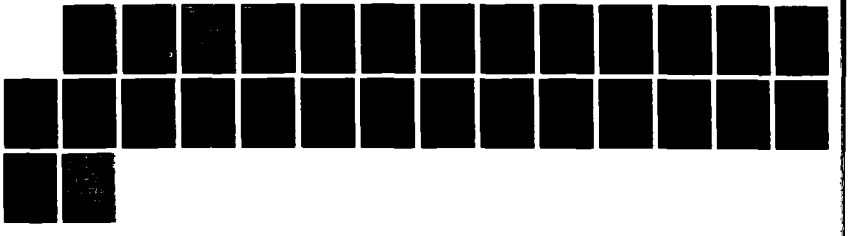

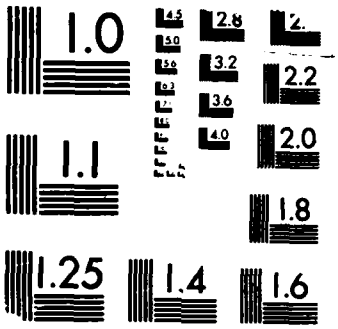

ARO 22382.20-CH

SUPER HYDRIDES

FINAL REPORT

Herbert C. Brown
Principal Investigator

March 15, 1985 - March 14, 1988

U. S. Army Research Office

Grant Number: DAAG-29-85-K-0062

Purdue University
West Lafayette, Indiana 47907

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18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The discovery of metal hydride reducing reagents has without exaggeration revolutionized the reduction of functional groups in organic chemistry. In the last decade or so asymmetric synthesis has emerged from the cold to vie quite successfully with enzymes as a means of incorporating chirality in prostereogenic centers. My group has been in the forefront of this second revolution in organic chemistry. During the course of our research for the period covered in this Final Report, we have made tremendous leaps forward, both in developing new chiral reducing reagents and in understanding their mode of reaction. In this regard we have concentrated our

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efforts in two major areas, 1) Chiral trialkylboranes and 2) Chiral borohydrides. In the first case we have discovered the extremely versatile and readily accessible asymmetric reducing reagent, diisopinocampheylchloroborane, Ipc_2BCl, derivable from α-pinene of either antipode. Our success with Ipc_2BCl in transferring stereogenicity to alcohols encouraged us to explore further modifications of the α-pinene moiety as useful chiral directors. In doing so we have developed new reagents, i.e., diethylapopinanylchloroborane, Eap_2BCl, which can rival enzymes in the degree of transfer of stereogenicity to suitable substrates, and which can out perform enzymes in scope.

In the second case we have succeeded in defining the limits of chiral borohydrides as stereogenic transfer reagents in the reduction, in particular, of α–keto esters. With the latter group we routinely attain high levels of enantiomeric excess, ≥ 95%.

Finally, we have embarked on a third route, as yet unexplored - the chiral reduction of azomethines (imines) and their derivatives with chiral metalhydrides. Initial results are encouraging, and if the past is a candid harbinger of the future, we can expect to attain equally *noble* results in this area of research.

Table of Contents

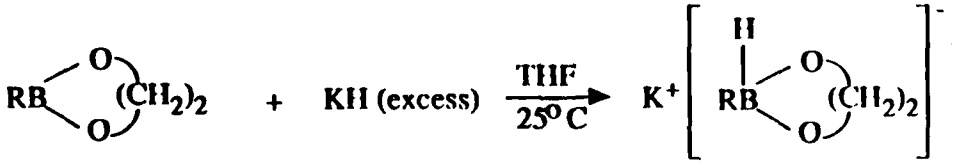
I. List of Participating Persons.

Name	Period of Appointment
W. S. Park	3/12/85 - 4/30/87
P. V. Ramachandran	3/15/85 - 1/31/88
B. T. Cho	5/1/85 - 1/31/87
B. Singaram	8/1/86 - 11/30/86
N. G. Bhat	9/1/86 - 10/31/86
M. V. Rangaishenvi	9/1/86 - 10/31/86
G. Rajendran	1/1/87 - 1/31/88
M. Zaidlewicz	5/1/87 - 5/30/87
M. Srebnik	7/1/87 - 12/31/87

II. Significant Results.

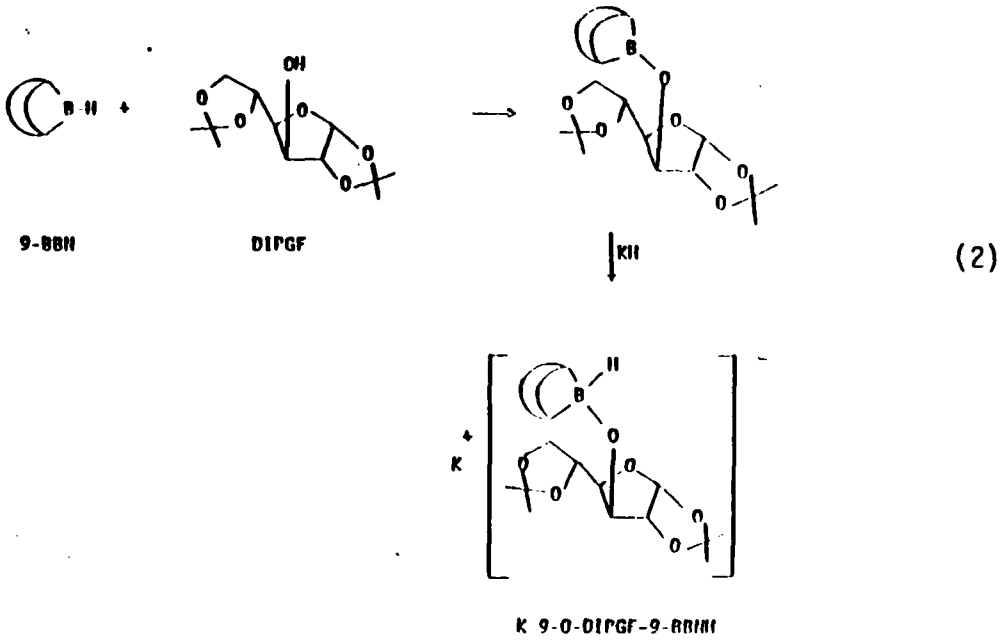
1. Asymmetric Reduction of the Carbonyl Group with Chiral Alkoxyborohydrides.

We have extended our synthesis of potassium dialkoxyborohydrides, $K^+[RB(OR')_2]^-$, conveniently prepared by the addition of excess potassium hydride to boronic esters, (eq 1)



(1)

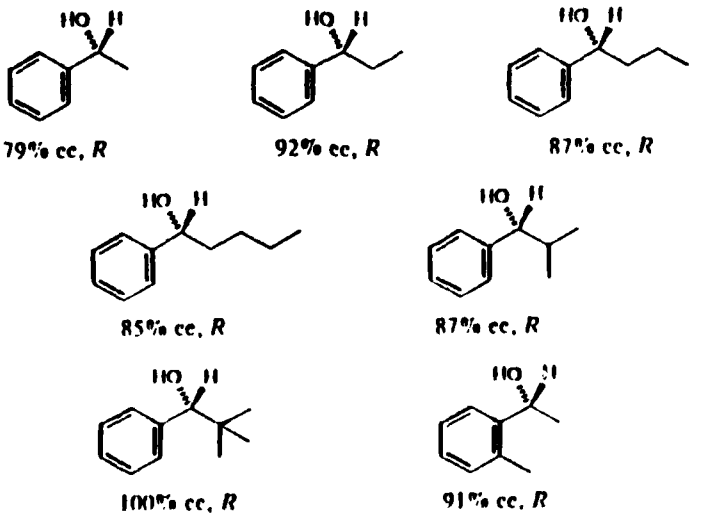
to include the new chiral reducing reagent, Potassium 9-O-(1,2:5,6-di-O-isopropylidene-α-D glucofuranose)-9-boratabicyclo[3.3.1]nonane, K-9-O-DIPGF-9-BBNH, K-Glucoride. (eq 2).



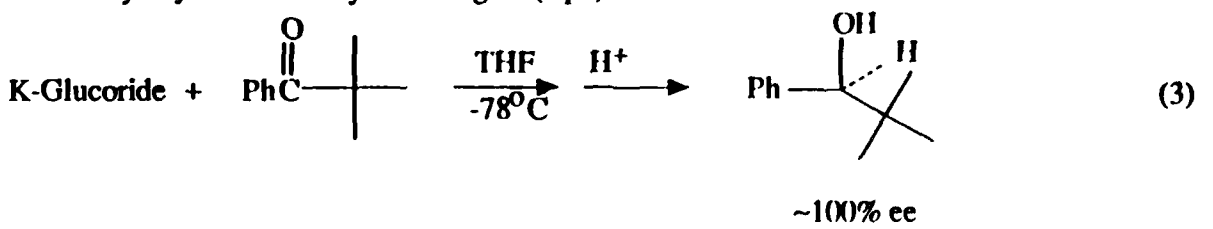
(2)

This stable easily prepared borohydride has been found to reduce cyclic and bicyclic ketones with a high degree of stereoselectivity. More importantly, K-Glucoride also reduces a variety of prostereogenic carbonyl compounds to the corresponding chiral alcohols in high ee. Thus aralkylketones are obtained with ee's approaching 100% (Table 1).

Table 1. Aralkyl Ketones Reduced with K-9-*O*-DIPGF-9-BBNH at -78°C



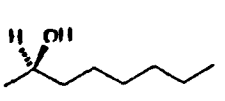
The reduction of pivalophenone with K-Glucoride has given one of the highest values obtained by any chiral borohydride reagent (eq 3).

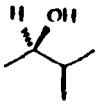


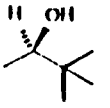
(3)

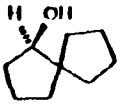
Hindered aliphatic ketones are also reduced to the aliphatic alcohols with high transfer of stereogenicity - amongst the highest reported in the literature for this kind of reagent (Table 2).

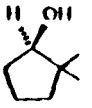
Table 2. Aliphatic Ketones Reduced with K-9-*O*-DIPGF-9-BBNH in THF at -78°C

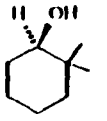

27% ee, *R*


36% ee, *R*


70% ee, *R*


82% ee, *R*


84% ee, *R*


61% ee, *R*

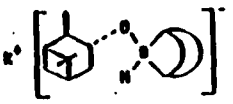
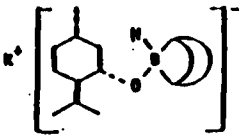
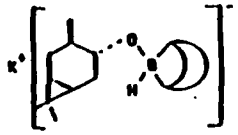
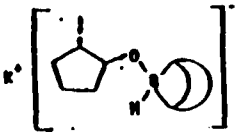
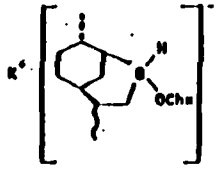
However, of particular significance is the reduction of α-keto esters which are reduced with very high enantiomeric excess, providing a wide range of chiral α-hydroxyesters in (Table 3).

Table 3. α-Keto Esters Reduced with K-9-*O*-DIPGF-9-BBNH in THF at -78°C

α-Keto ester	Time (h)	Yield (%)	% ee	Absolute configuration
Ethyl pyruvate	6	75	86	S
Ethyl 2-oxobutanoate	6	80	92	S
Ethyl 2-oxopentanoate	8	81	94	S
Methyl 3-methyl-2-oxobutanoate	8	83	98	S
Ethyl 3-methyl-2-oxobutanoate	8	85	97	S
Methyl 3,3-dimethyl-2-oxobutanoate	10	85	97	S
Ethyl 3,3-dimethyl-2-oxobutanoate	10	87	98	S
Ethyl 4-methyl-2-oxopentanoate	6	83	91	S
Methyl benzoylformate	10	85	92	S
Ethyl benzoylformate	10	80	94	S
Isopropyl benzoylformate	10	83	93	S
Ethyl α-oxo-1-naphthaleneacetate	10	78	96	S

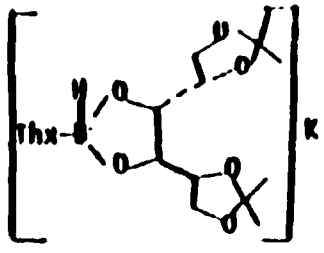
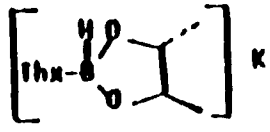
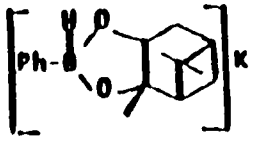
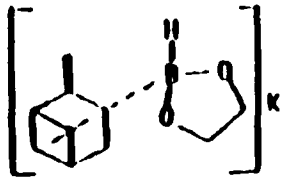
The alcohols are consistantly obtained with the same absolute configuration, making this reagent especially appealing for the preparation of compounds in which absolute stereochemistry is predictably incorporated. In related work we also prepared, in a manner similar to the preparation of K-Glucoride a series of new optically active monoalkoxyborohydrides with the chiral director centered on the ester moiety. The efficiency of these compounds to transfer stereogenicity in the reduction of two representative ketones, acetophenone and isopropyl methyl ketone was explored. The results are summarized in Table 4.

Table 4.

chiral borohydrides	acetophenone % ee, abs. config.	2-methyl-3-butanone % ee, abs. config.
	47 (S)	61 (S)
	12 (S)	40 (R)
	34 (R)	28 (S)
	26 (R)	37 (R)
	3 (R)	14 (R)

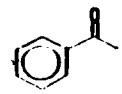
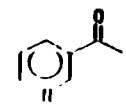
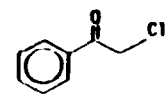
We next investigated the effect on optical induction in the reduction of ketones with chiral dialkoxyborohydrides in which the chiral director is centered primarily on the ester moiety (Table 5).

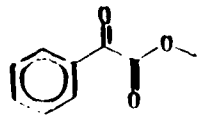
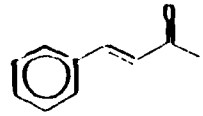
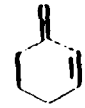
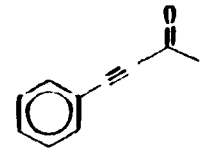
Table 5.

chiral borohydrides	acetophenone % ee, abs. config.	2-methyl-3-butanone % ee, abs. config.
	66 (*R*)	44 (*R*)
	9 (*S*)	13 (*R*)
 K-ThxBD-BH	5 (*R*)	14 (*S*)
	14 (*S*)	10 (*R*)

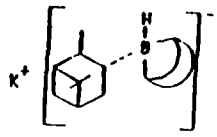
We then selected the best reagent in this series and compared it to K-Glucoride in the reduction of two representative ketones (Table 6).

Table 6. Comparison of Chiral Reduction with K-Glucoride and K-ThxBD-BH

reagent/ketone					
K-Glucoride	36% ee [*R*]	84% ee [*R*]	78% ee [*R*]	70% ee [*R*]	77% ee [*S*]
K-ThxBD-BH	44% ee [*R*]	0.3% ee [*R*]	74% ee [*R*]	56% ee [*R*]	16% ee [*S*]

				
K-Glucoride	92% ee [*S*]	60% ee [*R*]	1,4-Reduction	61% ee [*R*]
K-ThxBD-BH	25% ee [*S*]	15% ee [*R*]	71% ee [*S*]	35% ee [*S*]

Finally we developed a series of chiral trialkylborohydrides and chiral dialkylmonoalkoxyborohydrides based on readily available monoterpene chiral auxiliaries, and tested these reagents in the asymmetric reduction of two standard ketones: acetophenone and isopropyl methyl ketone. The results are summarized below.



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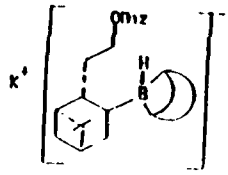

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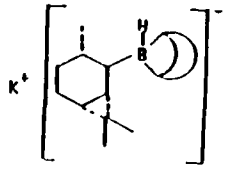

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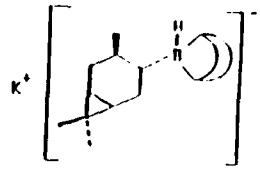

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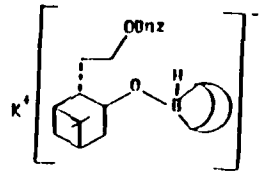

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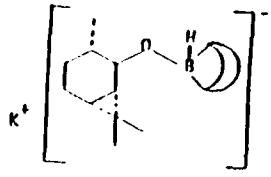


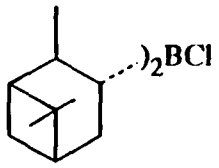
6

Reagent	% ee Acetophenone	Config.	% ee 3-Methyl-2-butanone	Config.
1	5	*R*	41	*R*
2	15	*S*	32	*S*
3	7	*S*	32	*S*
4	3	*S*	56	*R*
5	32	*R*	62	*R*
6	45	*R*	69	*R*

These results indicate that in general the chiral dialkylmonoalkoxyborohydrides give superior results. In particular, reagent 6 reduces 3-methyl-2-butanone in 69% ee.

2. Asymmetric Reductions of the Carbonyl Group with Chiral Dialkylchloroboranes.

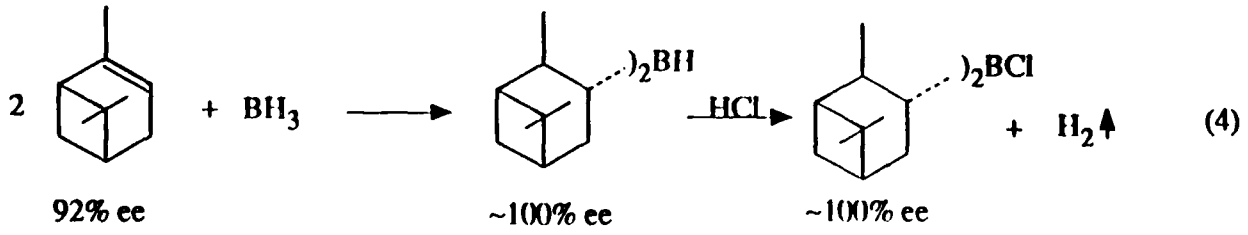
Various chiral trigonal boranes have been developed for the asymmetric reduction of the carbonyl group. However, in most cases the rates of reduction are slow and the enantioselectivities highly variable. In the course of our studies centered on developing new chiral reducing reagents we discovered that chiral dialkylhaloboranes, R^*_2Bx, (in particular chloroboranes), greatly increase the rates of reduction of the carboxyl group, presumably due to increased Lewis acidity of the boron atom and therefore, increased complexation (generally assumed to proceed the transition state), while at the same time maintaining high levels of stereogenicity transfer. In particular we have discovered that diisopinocampheylchloroborane, Ipc_2BCl, is an excellent chiral reducing reagent for a number of carbonyl functionalities.



$^d Ipc_2BCl$

The symbol "d" indicates that the reagent is derived from (+)-α-pinene.

Ipc_2BCl is readily available from either (+)- or (-)-α-pinene by hydroboration with BH_3·L followed by treatment of Ipc_2BH with HCl (eqn 4).



(4)

In the process of preparing Ipc_2BCl the product is optically upgraded from 92% ee to ~ 100% ee (eq 4).

Ipc_2BCl reduces prostereogenic aralkylketones in high enantiomeric excess. The results are summarized in Table 7.

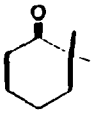
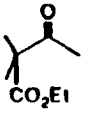
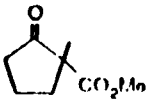
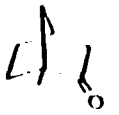
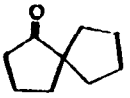
Table 7. Aralkyl Ketones Reduced with $^{d}Ipc_2BCl$ in THF at -25°C

Ketone	% ee	Product configuration
Acetophenone	98	S
2'-Acetonaphthone	98	S
3-Acetylpyridine	92	S
2-Acetylthiophene	91	S
Indanone	97	S
Propiophenone	98	S
Butyrophenone	98	S
Isobutyrophenone	78	S
Phenyl *t*-butyl ketone[a]	79	R

[a] Reaction was carried out at 25°C.

In addition to high ee's, the alcohols are obtained consistantly with known absolute configuration, S, from $^{d}Ipc_2BCl$. We have also discovered that α,α-dialkylketones can also be asymmetrically reduced with almost complete transfer of stereogenicity (Table 8).

Table 8. Asymmetric Reduction of Hindered Aliphatic Ketones with $^{d}Ipc_2BCl$ at 25°C

Ketone	% ee	Ketone	% ee
	95 (S)		91 (S)
	82 (S)		93[a]
	98 (S)[b]		89 (1S,2S)
	95 (S)		

[a] 96% ee for reaction at -25°C

[b] Based on analogy with reduction of spiro[4.4]nonan-1-one

More recently we have investigated the reduction of haloaralkylketones with Ipc_2BCl. The results were equally satisfying (Table 9).

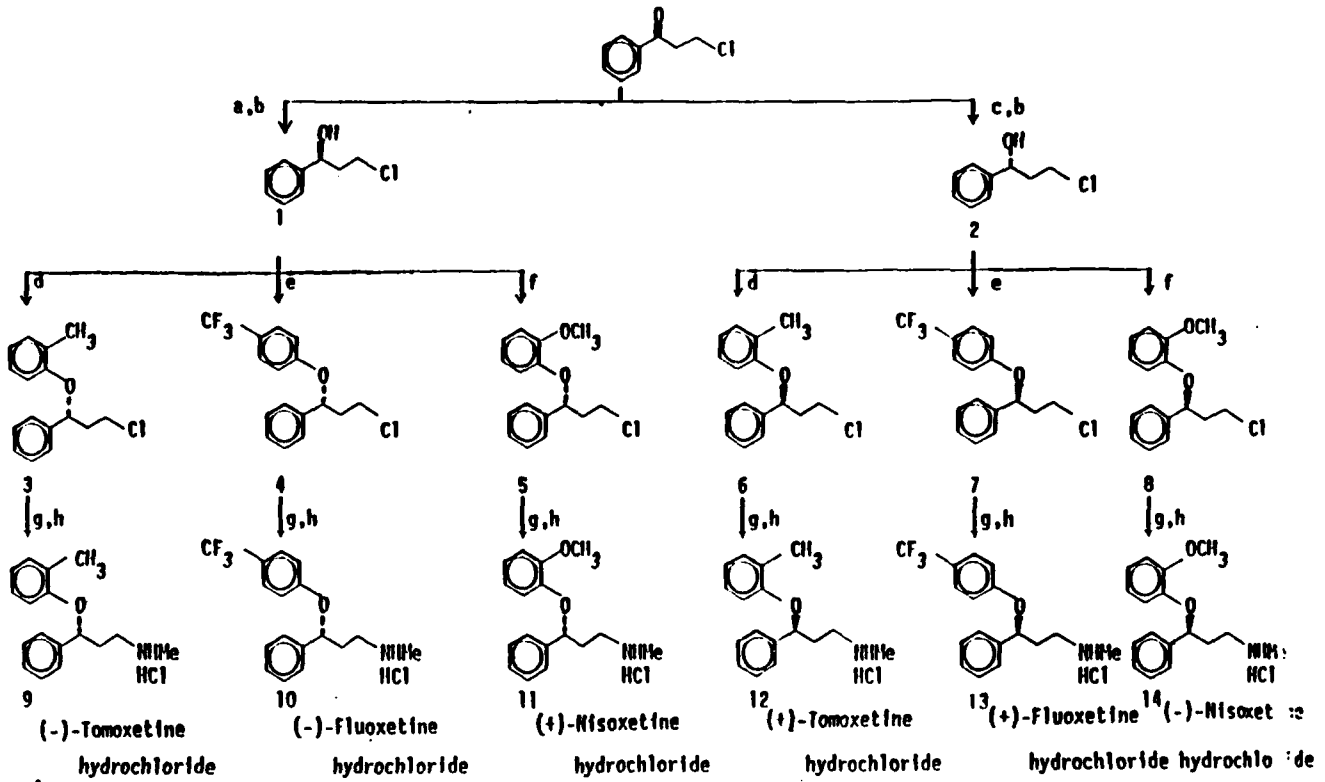
Table 9. Asymmetric Reductions of Haloaralkylketones with $^{d}Ipc_2BCl$ in THF at -25°C

	haloalcohol product		cyclized product
	% ee[a]	abs. config.	% ee
2-chloroacetophenone	96	*R*	96
2-bromoacetophenone	86[b]	*R*	86
2-iodoacetophenone	67[b]	*R*	67
2'-bromoacetophenone	99	(*S*)[c]	
4'-bromoacetophenone	97	(*S*)[c]	
3-chloropropiophenone	97	(*S*)[c]	
4-chloropropiophenone	98	(*S*)[c]	
2,2',4'-trichloroacetophenone	93	(*R*)[c]	
1-(4-bromophenyl)-4-chlorobutyrophenone	98	(*S*)[c]	98[d]

[a]Determined by capillary GC analysis of [*R*]-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetate. [b]Determined by conversion to the epoxide and measuring the rotation. [c]By analogy to the reduction of acetophenone and propiophenone. [d]By analogy to the cyclization of 2-chloroacetophenone.

Based on the above results we have developed a highly enantioselective synthesis of the clinically important anti-depressants, (-)-Tomoxetine, Fluoxetine (Prozac, Eli Lilly), and Nisoxetine (Scheme 1).

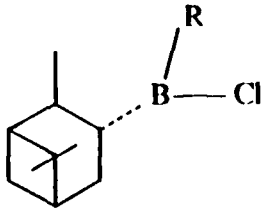
Scheme 1



a: $^{d}Ipc_2BCl$ (the symbol *d* refers to the reagent derived from (+)-α-pinene. b: Recrystallization. c: $^{l}Ipc_2BCl$ (the symbol *l* refers to the reagent derived from (-)-α-pinene). d: *o*-Cresol, DEAD, Ph_3P. e: *para*-trifluoromethylcresol, DEAD, Ph_3P. f: Guaiacol, DEAD, Ph_3P. g: Aqueous $MeNH_2$, EtOH. h: Ethereal HCl.

The key step in this synthesis was the asymmetric reduction of 3-chloropropiophenone with either $^{d}Ipc_2BCl$ or $^{l}Ipc_2BCl$ (the superscript "l" indicates that the reagent is derived from (-)-α-pinene) to furnish 1-chloro-3-phenyl-3-propanol in ≥ 97% ee. Recrystallization of the latter afforded the optically pure compound which was transformed to the propylamine anti-depressant as shown in Scheme 1. Another salient feature of this synthesis is that it correlated for the first time the absolute configuration of the enantiomers of Nisoxetine with their signs of rotation. Confusion had existed in the literature on this point prior to our work.

We have also systematically investigated the effect on enantioselectivity of substituting an achiral alkyl group for one Ipc moiety.



R= Me, Et, i-Pr, t-Bu, Thx.

The reduction of two representative ketones was investigated: acetophenone and isopropyl methyl ketone (Table 10).

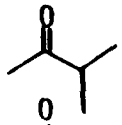
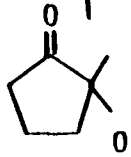
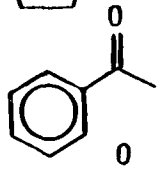
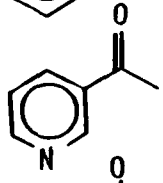
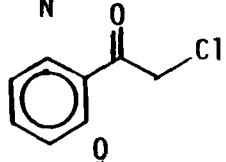
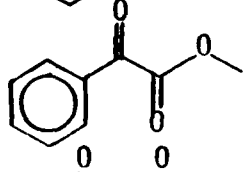
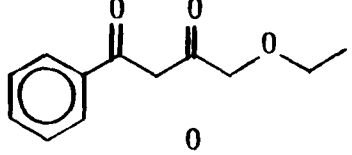
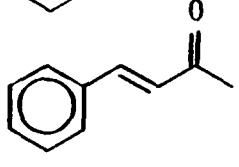
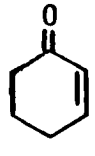
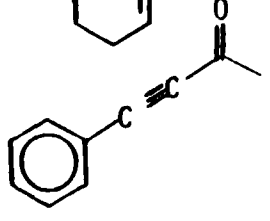
Table 10. Reduction of Acetophenone and Methyl Isopropyl Ketone with Monoisopinocampheylalkylhaloboranes, ^{d}IpcRBX, in Ethyl Ether

R	X	time h	temp °C	% ee and abs. config. of 1-phenyl-1-ethanol	% ee and abs.[a] config. of 3-methyl-2-butanol
Me	Cl	12	-25	15, *S*	48, *S*
Et	Cl	12	-25	33, *S*	36 *S*
i-Pr	Cl	12	-25	81, *S*	25, *S*
i-Pr	Br	12	-25	85, *S*	—
t-Bu	Cl	12	0	93, *R*	—
		48	-25	95, *R*	44, *S*
t-Bu	Br	24	-25	85, *R*	—
Thx	Cl	96	25	83, *R*	18, *S*

[a]Determined by capillary GC of the corresponding (+)-MTPA esters.

A consistant increase in optical induction (in the case of acetophenone) was observed with increasing steric requirements of the alkyl group. Particularly intriguing was the almost complete reversal of the absolute mode of reduction of acetophenone with ^{d}Ipc(t-Bu)BCl (95% ee, R) as compared with ^{d}Ipc$_2$BCl (97% ee, S). This prompted us to investigate the asymmetric reducing capacity of ^{d}Ipc(t-Bu)BCl in greater detail with a wider selection of ketones (Table 11).

Table 11. Reduction of Representative Ketones with ^{d}Ipc(*t*-Bu)BCl

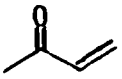
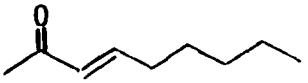
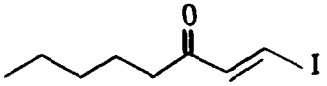
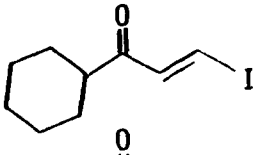
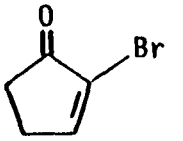
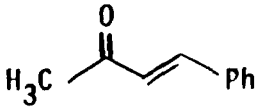
ketone	solvent, temp, °C	time h	% ee[c] abs. config.	% ee and abs. config. of ketones reduced with $^{d}Ipc_2BCl$
	EE, -25	12	44, *S*	32, *S*
	neat, 25	24	34, *R*	98, *S*
	EE or THF, -25	48	95, *R*	98, *S*
	THF, 25	168[b]	96, *R*	92, *S*
	EE, -25	24	98, *R*	95, *S*
	THF, -25	1	91, *S*	
	THF, -25	1	no reaction	
	EE, -25	24	85, *R*	14, *S*
	EE or THF, -25	24	46, *R*	36, *S*
	EE or THF, 25	5	21, *S*	21,

[a]Reactions were run at 0.5 *M* in the given solvent. [b]Two equiv of the reagents were used. [c]Determined by capillary GC of the corresponding (+)-MTPA esters.

Aromatic ketones, haloaralkylketones and α-ketoesters are reduced by Ipc(t-Bu)BCl with excellent transfer of stereogenicity. Of particular consquence is the reduction of *trans*-4-phenyl-3-buten-2-one (85% ee). In general α,β-unsaturated system have not fared well with asymmetric reducing reagents.

Our success with Ipc(t-Bu)BCl prompted us to investigate the utility of Ipc_2BCl in the asymmetric reduction of α,β-unsaturated ketones (Table 12).

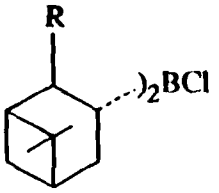
Table 12. Reduction of α,β-Unsaturated Ketones with [d] Ipc_2BCl in THF at -25°C

ketone	% ee	abs. config.
	64	*S*
	73	[*S*][a]
	85	*S*
	77	*S*
	88	[*S*][a]
	88	*S*

[a]By analogy to the reduction of the other compounds in the series.

These results are most encouraging. The β-Iodo-allylic alcohols in particular are important intermediates in the synthesis of prostaglandines. We plan to continue our systematic investigation of the reduction of enones with other chiral reducing reagents, in particular Ipc(t-Bu)BCl.

The pinany moiety has served well as a chiral director in the asymmetric reductions of the carbonyl group. But not all carbonyl groups are reduced in high ee. In an effort to increase still further the number of keto groups that can be chirally reduced in high ee we began a systematic investigation of modified pinanyl nucleus as chiral directors.

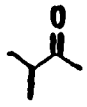
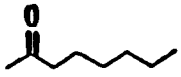
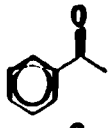
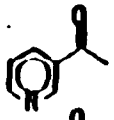
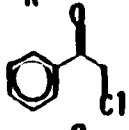
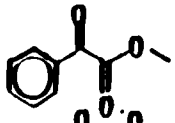
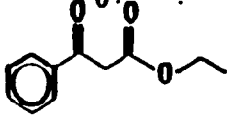
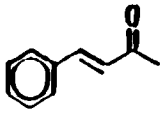
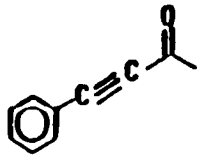


R= Et, i-Pr, t-Bu, Ph

The first compound we prepared in this series, ethylapopinanylchloroborane (R=Et), ^{l}Eapine$_2$BCl, has proven to be a particularly rewarding reagent (Table 13). With this reagent we have achieved complete transfer of stereogencity for many classes of ketones (Table 13), specifically, *secondary*-aliphatic, dialkylaliphatic, aralkylketone, and haloaralkylketones.

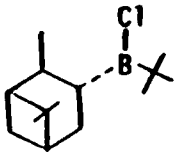
Several other asymmetric reducing agents based on ethylapopinene, such as ^{l}Eapine-9-BBN and lithium ^{l}Eapine-9-BBNH, have shown some promise in chiral reductions (Table 13).

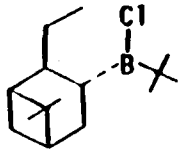
Table 13. Reduction of Representative Ketones with ^{l}Eapine-9-BBN,[a] Lithium ^{l}Eapine-9-BBN,[a] Borohydride, ^{l}Dieapine Chloroborane[a]

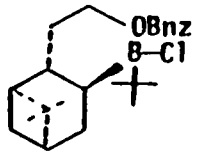
Ketone	^{l}Eapine-9-BBN % ee, abs. config.	Lithium ^{l}Eapine-9-BBNH Borohydride (-78°C) % ee, abs. config.	^{l}Dieapinechloroborane (-25°C) % ee, abs. config.
	37.4, *R*	64, *S*	100, *S*
	—	70,	—
	3, *R*	7.2, *S*	100, *S*
	78, *R*	56, *S*	100, *S*
	95.8, *R*	~ 2, *S*	100, *S*
	72.1, *S*	47.7, *R*	100, *S*
	90,	—	70, *R*
	—	—	no reduction
	—	—	81, *S*
	33, *R*	1,4-addition	74, *S*
	89, *R*	5.2, *S*	33, *R*

[a]The superscript "*l*" denotes that the ethylapopinanyl group is derived from (-)-nopol. [b]The superscript that the pinanyl group is derived from (+)-α-pinene.

The preparation of other compounds in this series and related reagents is in progress. We have also developed the synthesis of a series of hindered unsymmetrical halodialkylboranes. Among these, the reagent NopOBnzB(*t*-Bu)Cl provided highly promising results in the reduction of representative ketones.

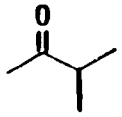




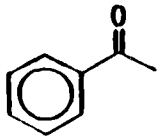


NopOBnzB(*t*-Bu)Cl

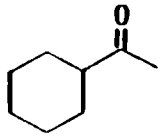
The results are as shown below.



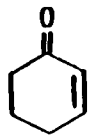
89.7% ee, [*R*]



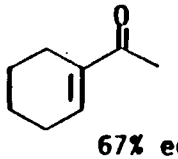
79% ee, [*S*]



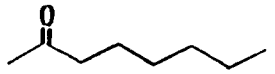
96.2% ee, [*R*]



88% ee, [*S*]



67% ee



40% ee, [*R*]

Particularly noteworthy here is the high levels of ee obtained in the reduction of aliphatic ketones, i. e., isoproply methyl ketone (~ 90% ee) and cyclohexyl methyl ketone (~96% ee), amongst the highest values reported in the literature.

3. A Comparative Rate Study of the Elimination of Alkenes from Dialkylhaloboranes.

Our success with Ipc_2BCl as a chiral reducing agent prompted us to explore in considerable detail the elimination of alkenes in the reaction of dialkylhaloboranes with benzaldehyde (eq 5).

$$R_2BX + PhCHO \xrightarrow{-alkene} RB(OBn)X \xrightarrow{-alkene} (BnO)_2BX \qquad (5)$$

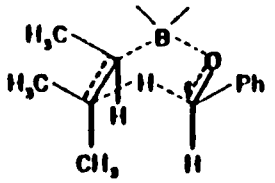
We found that, not unexpectedly, dialkylhaloboranes reduce benzaldehyde at a rate much faster than that of trialkylboranes. Whereas Ipc_2BCl reduces 2 equiv of benzaldehyde at room temperature almost instantaneously the related trialkylborane, Ipc_2B-*n*-hexane requires ~ 6 days. Sia_2BCl, $(2\text{-MeCpn})_2BCl$, Ipc_2BCl and Ipc_2BBr also reduce benzaldehyde rapidly, but $(2\text{-MeChx})_2BCl$ reacts more slowly (Table 14).

Table 14. Reaction of Dialkylhaloboranes and Trialkylboranes with Benzaldehyde at 25°C

reagent	solv	time for elimination of 1 equiv of alkene, min	time for elimination 2 equiv of alkene, m
Ipc_2BCl (1)	THF	<1	<1
Ipc_2B-*n*-Hex (3)	THF	<1	8640
Ipc_2B-*exo*-Nb (4)	THF	15	12960
Sia_2BCl (5)	CH_2Cl_2	<1	270
2-MeChx$_2$BCl (6)	THF	1320	—[a]
2-MeCpn$_2$BCl (7)	THF	<1	300
Car_2BCl (8)	THF	<1	15
Car_2B-*n*-Hex (9)	THF	<1	10080
Ipc_2BBr (10)	THF	<1	45

[a] A second mole of 1-methylcyclohexene was not eliminated, even on refluxing in CH_2Cl_2 for several hours.

These results are consistent with a cyclic boat-like transition state.

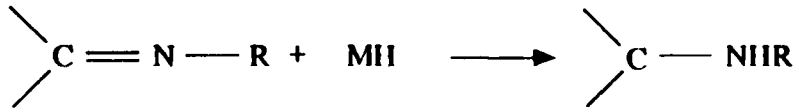


Transition-state model for the reduction of benzaldehyde with Sia_2BCl.

The present study has given us leads for future modifications of chiral boron reagents. Hopefully our insight into the nature of both electronic and steric factors will be expressed by new and even better chiral reducing reagents in the future.

4. Rate and Stoichiometry in the Reduction of Imines and Derivatives with Boron Hydride Reagents.

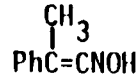
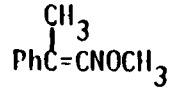
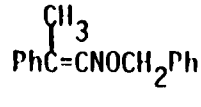
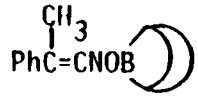
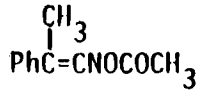
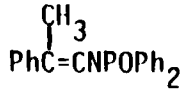
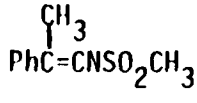
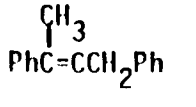
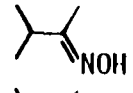
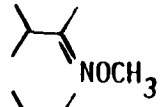
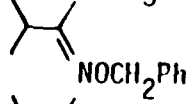
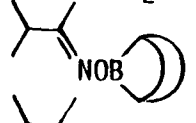
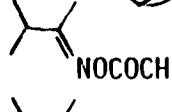
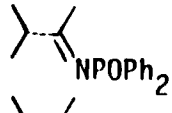
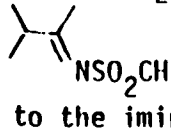
Sporadic and conflicting reports on the reduction of azomethines (imines) and their derivatives by hydride reagents has prompted us to undertake a systematic and detailed study of the reduction of these functional groups (eq 6).



(6)

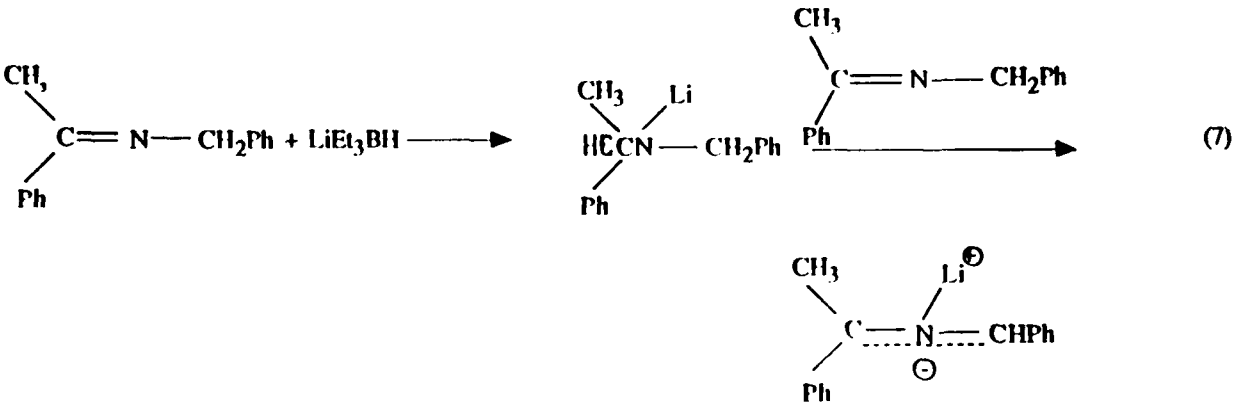
To broaden our understanding of this important chemical transformation, we have selected to investigate representative imine derivatives, aliphatic and aromatic, with a select list of acidic and nucleophilic boron hydride reducing agents, such as borane-THF (BH_3-THF), 9-borabicyclo[3.3.1] nonane (9-BBN), lithium borohydride ($LiBH_4$), and lithium triethylborohydride ($LiEt_3BH$). The results are summerized in Table 15.

Table 15. Reduction of Oxime and Imine Derivatives with Boron Hydride Reagents in THF at 25°C

No	substrate/reagent	BH_3	9-BBN	$LiBH_4$	$LiEt_3BH$
1		--		—	— —
2		+	--	--	-
3		+	--	--	-
4		+	--	+ +	--
5		-	-	--	--
6		+ +	+ +	+ +	+ +
7		+	+ +	+ +	+ +
8		+ +	+ +	+ +	±[a]
9		-		-	--
10		+	-	--	-
11		+	-	--	-
12		+	--	++	--
13		-	-	--	--
14		++	++	++	++
15		+	++	++	++

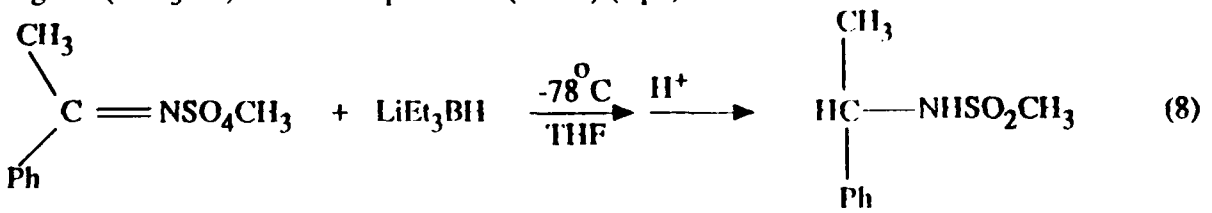
+ Reduction to the imine in ~ 24 h. ++ Reduction is rapid and complete in < 1 h at 25°C. - Slow and partial reduction. -- No reduction. [a]The reduction is fast, but stops at 50% conversion.

We have found that the imine derivatives generally undergo facile reduction at a rate faster than that of oxime derivatives. For instance, compounds 6, 7, 8, 14 and 15 (Table 15) are reduced by most of there reagents in about 10 min at 25°C. However, imines 7 and 15 (Table 15) need 24 h for reduction with BH_3·THF and compound 8, is reduced with $LiEt_3BH$ in only 50% conversion. This may be due to a facile lithiation of the imine by the newly found lithium amide. (eq 7).



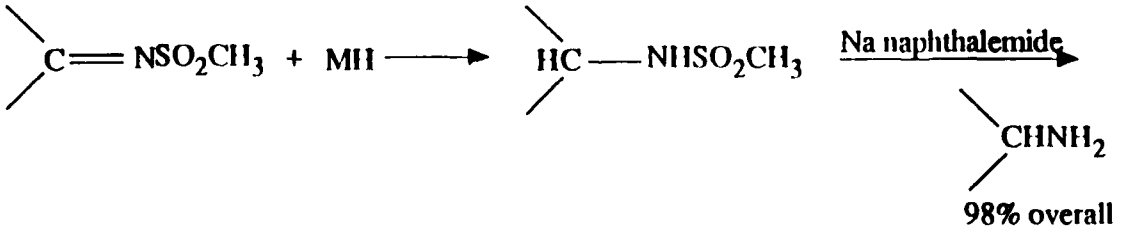
(7)

A particularly promising activated imine derivative appears to be the N-sulfonylimines. We have disconered that these derivatives are rapidly reduced by nucleophilic hydride reducing reagents ($LiEt_3BH$) at low termperatures (-78°C) (eq 8).



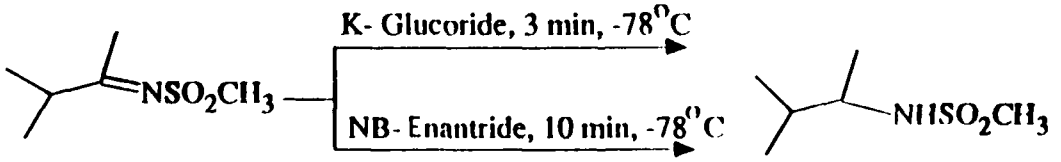
(8)

Since the N-sulfonylamines can be cleaved by *inter alia*, sodium naphthalemide, to the free amine, we have in essence developed a convenient two-step procedure for the synthesis of amines (eq 9)



(9)

Fast reduction at low temperatures, and subsequent facile cleavage to the free amine, make N-sulfonylimines attractive candidates for asymmetric reduction. We have initiated studies in that direction. For instance, (K-Glucoride and NB-Enantride reduce compound 15 (Table 15) in 3 min and 10 min respectively at -78°C (eq 10).



(10)

Further work on the asymmetric reduction of this class of activated imines is in progress.

III. List of Publications.

This is a continuation of the list submitted with the last Final Report, Grant-29-82-K-0047, for the period 2/1/82 - 1/31/85. The required number of reprints for each of the publications has been included in the Semi-annual Reports.

1. Hydroboration. 70. The Polycyclic Hydroboration of Acyclic and Cyclic Trienes with Borane in Tetrahydrofuran and Trimethylamine Borane. Reexamination of the Stereochemistry of Isomeric Perhydro-9*b*-boraphenalenes
   H. C. Brown, E. Negishi and W. C. Dickason
   J. Org. Chem., 50, 520 (1985)
2. Addition Compounds of Alkali Metal Hydrides. 27. A General Method for Proparation of the Potassium 9-Alkoxy-9-boratabicyclo[3.3.1]nonanes. A New Class of Stereoselective Reducing Agents
   H. C. Brown, J. S. Cha, B. Nazer and C. A. Brown
   J. Org. Chem., 50, 549 (1985)
3. Diisopinocampheylchloroborane, A Remarkably Efficient Chiral Reducing Agent for Aromatic Prochiral Ketones
   J. Chandrasikharan, P. V. Ramachandran and H. C. Brown
   J. Org. Chem., 50, 5446 (1985)
4. Hydroboration. 73. Relative Rates of Hydroboration of Representative Heterocyclic Olefins with 9-Borabicyclo[3.3.1]nonane
   H. C. Brown, P. V. Ramachandran and J. V. N. Vara Prasad
   J. Org. Chem., 50, 5583 (1985)
5. Addition Compounds of Alkali Metal Hydrides. 28. Preparation of Potassium Dialkoxymonoalkylborohydrides From Cyclic Boronic Esters. A New Class of Reducing Agents
   H. C. Brown, W. S. Park, J. S. Cha, B. T. Cho and C. A. Brown
   J. Org. Chem., 51, 337 (1985)
6. Potassium 9-*O*-(1,2:5,6-Di-*O*-isopropylidene-α-*D*-glucofuranose)-9-boratobicyclo[3.3.1]nonane. A New, Effective Chiral Boragydride Reagent
   H. C. Brown, W. S. Park and B. T. Cho
   J. Org. Chem., 51, 1934 (1986)
7. Addition Compounds of Alkali Metal Hydrides. 29. Preparation and Properties of Chiral Dialkylmonoalkoxyborohydrides. A New Class of Asymmetric Reducing Agents
   H. C. Brown, W. S. Park and B. T. Cho
   J. Org. Chem., 51, 3278 (1986)
8. Highly Efficient Asymmetric Reduction of α-Tertiary Alkyl Ketones With Diisopinocampheylchloroborane
   H. C. Brown, J. Chandrasekharan and P. V. Ramachandran
   J. Org. Chem., 51, 3394 (1986)
9. Asymmetric Reduction of α-Keto Esters With Potassium 9-O-(1,2:5,6-di-O-Isopropylidene-α-D-glucofuranose)-9-boratabicyclo[3.3.1]nonane. Chiral Synthesis of α–Hydroxy Esters With Optical Purity Approaching 100% ee
   H. C. Brown, B. T. Cho and W. S. Park
   J. Org. Chem., 51, 3396 (1986)
10. Organoboranes. 47. An Extremely Facile Elimination of Alkenes From Dialkylhaloboranes. A Comparative Rate Study With Related Trialkylboranes

H. C. Brown, P. V. Ramachandran and J. Chandrasekharan
Organometallics, 5, 21d38 (1986)

11. Addition Compounds of Alkali Metal Hydrides. 31. Preparation and Properties of Chiral Dialkyxymonoalkylborohydrides. A New Class of Asymmetric Reducing Agents
H. C. Brown, B. T. Cho and W. S. Park
J. Org. Chem., 52, 4020 (1987)
12. Addition Compounds of Alkali Metal Hydrides. 32. A Comparison Study of Chiral Trialkylborohydrides and Chiral Dialkylmonoalkoxyborohydrides for the Asymmetric Reduction of Prochiral Ketones: The Effect of Comparable Chiral Alkyl and Alkoxy Groups on Asymmetric Induction
H. C. Brown, W. S. Park and B. T. Cho
Bull. Korean Chem. Soc., 8, 276 (1987)
13. Selective Reductions 39. The Partial Reduction of Carboxylic Acids With Thexylchloroborane-Methyl Sulfide. A Direct and Simple Aldehyde Synthesis
H. C. Brown, J. S. Cha, N. M. Yoon and B. Nazer
J. Org. Chem., 52, 5400 (1987)
14. Selective Reductions. 40. A Critical Examination of the Relative Effectiveness of Various Reducing Agents for the Asymmetric Reduction of Different Classed of Ketones
H. C. Brown, W. S. Park, B. T. Cho and P. V. Ramachandran
J. Org. Chem., 52, 5406 (1987)

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